DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NOV 7 2005

The Honorable Tom Davis
Chairman
Committee on Government Reform
House of Representatives
Washington, D.C. 20515-6143

Dear Mr. Chairman:

Thank you for your October 21, 2005, letter concerning a *Washington Post* article reporting that five products marketed as dietary supplements were tested and allegedly found to contain anabolic steroids. The Food and Drug Administration (FDA or the Agency) shares your concern about the use of steroids among adolescents and the apparent increase in so-called designer steroid production and use.

In order to meet your deadline, we are providing a general response to your questions today. After you have a chance to review the information in this letter, if you are interested in additional details, we will be happy to arrange a briefing for you. Please note that this letter contains trade secret, commercial confidential, or other privileged information protected from disclosure to the public under the Freedom of Information Act (Title 5, United States Code [U.S.C.] section 552), the Trade Secrets Act (Title 18 U.S.C. section 1905), and FDA regulations. The Committee should not publish or otherwise make public such information. We would be glad to discuss with the Committee staff the protected status of any specific information.

FDA is investigating the five steroid products from the *Washington Post* article mentioned in your letter. We have spoken with Dr. Catlin of the United States Olympic drug testing lab at UCLA and an FDA investigative team will be visiting him to gather evidence concerning the analyses conducted on these products. We will consider enforcement and other options as part of the Agency's investigation of this matter once this evidence has been evaluated. Since the *Post* article was published, two of the five manufacturers appear to have discontinued their products, according to their public statements. FDA will continue the current investigation, including verifying information, obtaining samples as appropriate, and determining what,if any, additional testing is needed.

In evaluating a given product that may contain an anabolic steroid, the first task is to confirm whether or not an anabolic steroid is present. Establishing and validating analytical methods to test for steroids, steroid precursors, and chemically altered so-called designer steroids in products marketed as supplements, which often contain other ingredients, presents a scientific challenge. Hundreds of possible chemical entities are involved, and more substances are being "designed" every day by entrepreneurial marketers. As you know, FDA's staff and

financial resources are limited, so we must set priorities when making decisions about enforcement action.

After FDA has confirmed that an anabolic steroid is present, the next step is to determine how the product that contains the steroid should be regulated under the Federal Food, Drug, and Cosmetic (FD&C) Act. According to the *Washington Post* article, the five products discussed in the article are being marketed as dietary supplements. However, how a manufacturer or distributor chooses to market a product does not necessarily determine its classification under the FD&C Act. A product marketed as a dietary supplement may be properly regulated as such, or it may be subject to regulation as a drug, depending on its ingredients, labeling and other evidence of intended use (e.g., advertising), route of administration, and other factors relevant to the dietary supplement definition, such as whether there is an approved new drug application (NDA) or investigational new drug application for the product or one of its active ingredients.

The products discussed in the *Washington Post* article appear to be subject either to the new drug provisions of the FD&C Act or to the new dietary ingredient (NDI) notification requirements added to the FD&C Act by the Dietary Supplement Health and Education Act (DSHEA) of 1994. [redacted]

Because many steroid products are marketed as dietary supplements, some information on FDA's dietary supplement authority may be helpful as background. You asked specifically about dietary supplements that contain NDIs. An NDI is defined as a dietary ingredient that was not marketed in the United States before October 15, 1994. If the NDI has been "present in the food supply as an article used for food in a form in which the food has not been chemically altered," dietary supplements that contain it may be marketed without prior notification to FDA. If this is not the case, the FD&C Act requires the manufacturer or distributor to notify FDA 75 days prior to the marketing of the dietary supplement containing the NDI. The NDI notification must include the information upon which the manufacturer or distributor has based its conclusion that the dietary supplement containing the NDI will reasonably be expected to be safe. Failure to file an NDI notification when one is required causes the product to be adulterated under the FD&C Act.

In November 2004, FDA's Center for Food Safety and Applied Nutrition (CFSAN) held a public meeting and asked stakeholders the most efficient way for FDA to enforce the NDI provision of DSHEA and what the Agency's next steps should be in guidance and/or rulemaking to the industry. CFSAN published a public notice soliciting comments, and is reviewing all the comments received on this issue.

Except for products that are subject to the NDI notification requirement, FDA's regulation of dietary supplements is primarily a post-market program, like much of food regulation under the FD&C Act. There is no pre-market approval requirement for dietary supplements and there are no legally required monograph or other such standards for dietary supplements or their ingredients. Further, for the great majority of dietary supplements that do not contain

NDIs subject to the notification requirement, there is no requirement for the manufacturer to provide FDA with evidence about the safety of the product either before or after marketing.

By contrast, drug regulation involves an extensive pre-market evaluation of safety and effectiveness with detailed standards of evidence prescribed by statute and regulation. This evaluation provides a basis to guide not only approval decisions, but also how conditions of use should be limited to manage benefits and risks. In addition, there are post-market reporting requirements for drugs to support product safety monitoring. These requirements do not exist for dietary supplements.

Under DSHEA, then, we must rely on voluntary adverse event reports as a major component of our post-market regulatory surveillance efforts. Voluntary reporting systems are estimated to capture only a small percentage of adverse events, but they provide valuable signals of potential problems. When such a signal identifies a possible safety hazard, the burden is on FDA to gather and evaluate any scientific literature or information regarding whether the substance produces a safety hazard.

Your letter asks whether FDA's MedWatch system has received adverse event reports for anabolic steroid products marketed as dietary supplements. MedWatch is an Agency-wide program for voluntary and mandatory reporting of adverse events, quality problems, and use errors that are suspected to be associated with FDA-regulated products. When the MedWatch reporting program receives a report for a CFSAN-regulated product, the report is forwarded to CFSAN. In June 2003, CFSAN established the CFSAN Adverse Event Reporting System (CAERS) to monitor and analyze these adverse event reports for foods, cosmetics, and dietary supplements. There is no mandatory reporting requirement for adverse events associated with the use of dietary supplements. The voluntary adverse event reports submitted to CAERS vary in the quality and reliability of information provided. Information is recorded as reported, and therefore, the accuracy of symptom(s), product(s), amount(s) taken, and product ingredient(s) is dependent upon the quality of the report. Report quality may vary based on the information available to the reporter and the accuracy of his or her memory. (As resources permit, we follow up on reports, but these efforts are not always successful.) Furthermore, in many cases, individuals may have used more than one product around the time of the adverse event, and many products contain multiple ingredients. These variables complicate the evaluation and attribution of adverse events. Thus, there generally is no certainty that a reported adverse event can be attributed to a particular product or ingredient.

Another important aspect of FDA's regulatory and surveillance programs are to help ensure that dietary supplements are manufactured in a manner that will not result in adulteration. DSHEA gave FDA the authority to promulgate regulations prescribing current good manufacturing practice (cGMP) requirements or dietary supplements. These regulations will establish industry-wide standards to ensure that dietary supplements are not adulterated in certain respects. FDA has drafted a dietary supplement cGMP final rule, but it has not yet been published. On October 25, 2005, the draft rule was submitted to Office of Management and Budget (OMB), and is currently under OMB review. Until a final rule on dietary supplement cGMP is published and becomes effective, dietary supplement manufacturers are

subject to the requirements specified in Title 21, *Code of Federal Regulations*, part 110, Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Human Food.

With regard to your question about FDA's enforcement of labeling requirements for dietary supplements, FDA has a post-market surveillance program for this purpose. This compliance program, Dietary Supplements - Import and Domestic (copy enclosed), contains guidance to FDA field offices regarding field exams and sample collections to determine compliance with the labeling requirements for dietary supplements. Our regulatory efforts are currently focused on eight areas of emphasis outlined in the Compliance Program document. Significant violations of the labeling requirements for dietary supplements may lead to an advisory action, such as a Warning Letter, or to a court action for seizure or injunction. Imported products that do not comply with FDA labeling requirements are subject to detention and refusal when offered for entry into the United States.

In your October 21, 2005, letter, you ask how FDA works with other law enforcement agencies when we discover illegal steroid products marketed as dietary supplements. FDA works closely with the Drug Enforcement Administration (DEA) in this area. One success of our collaborative efforts was the passage of the Anabolic Steroid Control Act (ASCA) of 2004. The ASCA scheduled androstenedione (an anabolic steroid precursor) and a number of other substances under the Controlled Substances Act (CSA). The new law also authorized DEA to undertake an administrative scheduling process for new steroid ingredients. However, since the passage of that statute, regulators and law enforcement officials have seen an increase in the number of "designer" steroids that are being marketed in an attempt to evade the CSA's restrictions on controlled substances. Even with the passage of the ASCA, it takes time to identify new ingredients and new products in the marketplace, and it takes time to implement the scheduling of new substances through the administrative process.

With regard to regulation of dietary supplements, FDA coordinates with the Federal Trade Commission (FTC). FDA regulates the safety, manufacturing, and labeling of dietary supplements, while the FTC has primary responsibility for regulating the advertising of these products. Over the last few years, FDA and FTC have worked well together to ensure that there is a seamless assertion of federal jurisdiction over these products.

When criminal sanctions may be warranted, FDA's Office of Criminal Investigations (OCI) gets involved. OCI is the entity within the Agency responsible for the conduct and coordination of criminal investigations and, as such, maintains liaison and cooperative investigative efforts with other Federal, state, local, and international law enforcement agencies. OCI is instrumental in implementing FDA criminal investigation policy, training, and coordination. OCI uses all customary and legal criminal investigative techniques, interfaces directly with Federal and local prosecutorial offices and participates in grand jury proceedings and judicial actions as required.

At the core of FDA's enforcement efforts is our commitment to enhance the legitimate manufacture, sale, and use of dietary supplements while protecting consumers against unsafe products, fraudulent labeling claims, and other illegal practices. To achieve these goals, we utilize a number of strategies, including cooperation and coordination with other state,

Federal, and international law enforcement agencies in protecting consumers against unapproved and potentially harmful products offered by Internet outlets, some of which are based abroad. Since the passage of DSHEA, the number of dietary supplement products that are marketed within the United States has dramatically increased. It is very difficult for FDA to track each new dietary supplement product that enters the marketplace. Because of the great number and variety of dietary supplements and the many different ways they are marketed (e.g., at traditional retail stores, via catalogs, TV, and radio, and through foreign and domestic sources over the Internet), significant expenditure of resources is required to provide meaningful continuing surveillance.

FDA recognizes that traditional enforcement actions and coordinated efforts with other agencies are necessary, but these steps are not the only components of a thoughtful enforcement strategy. We fully appreciate that the dietary supplement industry has a vested interest in curbing fraudulent operators and practices, and that most of FDA's regulated industries are interested in complying with the FD&C Act, and do so. For this reason, FDA will continue in its efforts to complement these measures with industry and consumer education and will continue to assist the industry by issuing regulations and guidance documents addressing the manufacture, labeling, and sale of dietary supplements and other FDA-regulated products.

Again, let me assure you that we share your concern when we read newspaper articles about anabolic steroid products marketed as dietary supplements. We hope this response has been helpful to you. Please feel free to contact us if you need further information.

Sincerely,

Patrick Ronan

Patrick Ronan
Associate Commissioner
for Legislation